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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 01292004

Application Number: 09/766,366
Filing Date: January 18, 2001
Appellant(s): HILLMAN ET AL.

Richard C. Ekstrom and Joel Harris
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 11/10/2003.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief. Although there are no directly related appeals, it is noted that the issue of "specific binding" by an antibody is also addressed in USSN 09/520,941.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct. It is noted that claim 28 is both rejected and objected to.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is substantially correct. The changes are as follows:

Applicant includes in Issue 1 whether claims 25 and 33-37 are anticipated by Liu et al. under 35 U.S.C.§ 102(a). However, the Final Rejection of 5/1/03 included only claims 10, 26, 28 and 30-32 as anticipated by Liu et al. under 35 U.S.C.§ 102(a).

(7) Grouping of Claims

For Issue 1: The rejection of claims 10, 25-26, 28 and 30-37 stand or fall together because appellant's brief does not include a statement that this grouping of claims does not stand or fall together and reasons in support thereof. See 37 CFR 1.192(c)(7).

For Issue 2: The rejection of claims 10, 26, 28 and 33-35 stand or fall together because appellant's brief does not include a statement that this grouping of claims does not stand or fall together and reasons in support thereof. See 37 CFR 1.192(c)(7).

For Issue 3: The rejection of claims 25, 36 and 37 stand or fall together because appellant's brief does not include a statement that this grouping of claims does not stand or fall together and reasons in support thereof. See 37 CFR 1.192(c)(7).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

Liu et al., "Binding of HIV-I Nef to a Novel Thioesterase Enzyme Correlates with Nef-mediated CD4 Down-regulation" J. Biol. Chem., vol. 272, no. 21 (May 23, 1997), pp. 13779-13785

Zola, H. "Monoclonal Antibodies: A Manual of Techniques, CRC Press, Boca Raton, Florida 1987, "Introduction" pp. 1-11

(10) Grounds of Rejection

The following grounds of rejection are applicable to the appealed claims:

Issue 1:

Claims 10, 26, 28 and 30-32 stand rejected under 35 U.S.C. 102(a) as being anticipated by Liu et al. (J. Biol. Chem. May 23, 1997; 272(21):13779-13785, of record, see entire document), as evidenced by the attached alignment of SEQ ID NO:1 and SWISS-PROT accession # O14734, of record but also provided as an attachment for convenience.

Liu et al. teach the cloning and characterization of the thioesterase hTE, a protein found to interact with the HIV-1 Nef protein (see entire document, especially Fig. 2 and discussion). As evidenced by the attached alignment, residues 19-319 of hTE are identical to residues 11-311 of the instant polypeptide of SEQ ID NO:1. In addition the query match between the polypeptide of SEQ ID NO:1 and hTE is 97.3%.

Liu et al. also teach the production of a polyclonal antibody to the hTE protein produced by immunizing rabbits with a fragment of hTE from Q304 to K318 (i.e., the peptide QEGVIRVKPQVSESK); the affinity purification of the antisera on hTE; and the formulation of the antisera in a composition comprising an acceptable excipient/suitable carrier (Tris neutralized glycine HCl) (see e.g., page 13780 "Co-immunoprecipitation Experiments in CEM Cells Expressing HIV-1 NefLai" and Figure 2). It is also noted that an antisera is itself is a composition comprising an antibody and an acceptable excipient.

Since the antisera of Liu et al. specifically binds a protein identical to instant SEQ ID NO:1 from residue 11-311, the antisera of Liu et al. that specifically binds hTE meets the limitations of an isolated antibody which specifically binds a polypeptide comprising the amino acid sequence of SEQ ID NO:1.

The peptide used to produce the antisera of Liu et al. is present in both the hTE polypeptide of Liu et al. and instant SEQ ID NO:1. As noted supra, the antisera of Liu et al. binds the hTE polypeptide, indicating that the sequence of amino acids used in the immunizing peptide is available for binding in the context of the polypeptide. Because the sequence of the immunizing peptide is 100% conserved between the hTE polypeptide of Liu et al. and instant SEQ ID NO:1; the polyclonal antibody in the antisera of Liu et al. must necessarily bind the polypeptide of SEQ ID NO:1 which comprises this same sequence.

Liu et al. further teach using the antisera to detect hTE associated with Nef in western blots (e.g., Figure 4). The Materials and Methods associated with Figure 4 (e.g., page 13780, "Co-immunoprecipitation Experiments in CEM Cells Expressing HIV-1 NefLai") further teach detection of the anti-hTE antibody using an enhanced chemiluminescence system. Thus Liu et al. also teach a composition comprising the antibody wherein the antibody is labeled, since the anti-hTE and label of the chemiluminescence system are also a composition, and the chemiluminescence system acts as a "label" for the anti-hTE antibody.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the anti-hTE antibody of Liu et al.

The reference teachings thus anticipate the instant claimed invention.

Issue 2:

Claims 10, 26, 28 and 33-35 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al. (J. Biol. Chem. May 23, 1997; 272(21):13779-13785, of record), in view of Zola (Monoclonal Antibodies: A Manual of Techniques, CRC Press, Boca Raton, Florida 1987, "Introduction" pages 1-11, of record).

The claims are drawn to a *monoclonal* antibody to a polypeptide comprising the amino acid sequence of SEQ ID NO:1, methods of making, and compositions comprising said antibody.

As discussed in detail supra, Liu et al. teach an antisera comprising polyclonal antibody that specifically binds a protein identical to instant SEQ ID NO:1 from residue 11-311. For the reasons set forth supra, the antisera of Liu et al. meets the limitations of an isolated antibody which specifically binds a polypeptide comprising the amino acid sequence of SEQ ID NO:1.

Liu et al. do not teach *monoclonal* antibodies to a polypeptide comprising the amino acid sequence of SEQ ID NO:1, methods of making, or compositions comprising said antibody.

However, Zola teaches production of monoclonal antibodies using techniques well known in the art at the time the invention was made (e.g., see "Title"). Zola compares in Chapter 1 monoclonal antibodies and polyclonal antibodies (antisera). Zola concludes that monoclonal antibodies are advantageous over conventional antisera when the two antibody sources are compared, and further that monoclonal antibodies can be used in situations where polyclonal antisera would not even be considered (page 9, 3rd paragraph). In particular Zola notes that monoclonal antibodies provide both an opportunity for standardization and an unlimited source of reagent versus a polyclonal antisera (page 9 "V. Monoclonal Antibodies as Standard reagents").

In particular, Zola teaches immunizing an animal with an antigen of interest, isolating antibody producing cells from the animal, fusing the antibody producing cells with immortalized cells, culturing the resulting hybridoma cells, and isolating from the culture monoclonal antibody which binds the antigen of interest (summarized in Figure 4 on page 5).

Therefore, it would have been obvious to the ordinary artisan at the time the invention was made to prepare an anti-hTE monoclonal antibody using the basic immunization strategies taught by Liu et al. (which utilizes "an immunogenic fragment of instant SEQ ID NO:1", as set forth supra), or using the full length hTE polypeptide. The ordinary artisan would have been motivated to produce a monoclonal antibody to hTE to replace the polyclonal antisera of Liu et al. because, as taught by Zola, the ordinary artisan would have expected that, among other advantages, a monoclonal antibody would provide an indefinite and easily obtainable supply of antibody (as opposed to antisera). In addition, the ordinary artisan would have been motivated to provide the monoclonal antibodies in suitable carriers such as saline or Tris buffered glycine for use in the detection methods taught by Liu et al., or for other applications involving the monoclonal antibody, since placing antibodies in pharmaceutically acceptable carriers was well known in the art at the time the invention was made. Similarly, the ordinary artisan would have been motivated to label the monoclonal antibody for use in the detection method of Liu et al. in replacement of the polyclonal antisera.

Given the teachings of Liu et al. with respect to the antigen and in view of the art-recognized methodology as taught by Zola; the ordinary artisan would have had a reasonable expectation of producing a monoclonal antibody which, like the polyclonal antisera taught by Liu et al. would specifically bind the hTE polypeptide, which is identical to instant SEQ ID NO:1 from residue 11-311. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Issue 3:

Claims 25 and 36-37 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al. (J. Biol. Chem. May 23, 1997; 272(21):13779-13785, of record), in view of Zola (Monoclonal Antibodies: A Manual of Techniques, CRC Press, Boca Raton, Florida 1987, "Introduction" pages 1-11, of record), as applied to claims 10, 26, 28 and 33-35 above;
and further in view of Ramakrishnan et al. (US Pat. No. 5,817,310, of record).

The claims are drawn to various forms of an antibody and methods of making antibodies by screening recombinant immunoglobulin and Fab expression libraries.

Liu et al. each in view of Zola have been discussed previously and supra, and teach a monoclonal antibody to a polypeptide comprising an amino acid sequence of SEQ ID NO:1, methods of making and compositions comprising said antibody.

Liu et al. in view of Zola differ by not teaching chimeric, single chain, humanized or Fab/$F(ab')_2$ fragments of the antibody, nor by teaching that such antibodies can be isolated from Fab expression and recombinant immunoglobulin libraries.

However, one of ordinary skill in the art at the time the invention was made recognized that there were many ways to produce an antibody, and that the various forms of antibody were art-recognized variants of one another.

For example, Ramakrishnan et al. teach that the ordinary artisan at the time the invention was made recognized that antibodies could be formulated in any of a variety of interchangeable forms for use as compositions comprising a pharmaceutically acceptable carrier in a variety of art recognized assays to detect a protein of interest (see entire document, especially columns 8-17). Ramakrishnan et al. teach that

antibodies can be single chain antibodies, Fab fragments, or $F(ab')_2$ fragments (see e.g. column 9 at lines 9-27), as well as chimeric antibodies (e.g., column 14).

Ramakrishnan et al. also teach that it was well known in the art that antibodies to a protein of interest could produced by screening a recombinant immunoglobulin library which encode either the antibodies or fragments thereof (i.e. Fab) (e.g., see column 12 at line 56 to column 13). Further, compositions comprising antibodies in a pharmaceutically acceptable carrier, and various art recognized applications of antibodies for detection are taught in columns 15-17. Labeling of antibodies for use in various applications is also taught (e.g., column 11).

Therefore, it would have been obvious to the ordinary artisan at the time the invention was made to prepare antibodies in any of the instantly recited forms for use in art-recognized assays such as those of western blotting as taught by Liu et al.

The ordinary artisan would have been motivated to make these various forms of antibodies in view of the art-recognized interchangeability of the different antibody forms and in order to provide a variety of detection reagents that could be used in detection assays such as the western blotting assay taught by Liu et al.

The ordinary artisan recognized the advantage of antibody variants for use in such detection assays because depending upon the other antibodies used in combination, the antibody variants could be labeled using differential secondary reagents, thus avoiding high backgrounds in immunofluorescence and immunoblotting assays. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

(11) Response to Argument

Issue 1: Rejection under 35 U.S.C. §102(a)

Appellant argues that the Examiner has misinterpreted the claims by ignoring the claim recitation that the antibody "specifically binds" the recited polypeptide. Brief page 4, 3rd paragraph. Appellant argues that an antibody that "specifically binds" the polypeptide of SEQ ID NO:1 will distinguish between SEQ ID NO:1 and other polypeptides because the common usage of "specific" is "pertaining to, characterizing or distinguishing a species". Brief page 4, 4th and 5th paragraphs. Appellant further argues that because there are a differences between the amino acid sequence of SEQ ID NO:1 and the polypeptide of Liu et al., the antisera of Liu et al. cannot anticipate the instantly recited antibody because it binds the polypeptide of Liu et al.

Appellant attempts to interpret the claim language in such a way as to limit the recitation of an antibody that "specifically binds" to a polypeptide to an antibody that ONLY binds the recited polypeptide. Appellant acknowledges that the antisera of Liu et al. may bind the instantly recited polypeptide. Brief page 4 at 4th paragraph. Appellant by argument attempts to limit an antibody that "specifically binds" to a polypeptide to exclude binding to other polypeptides that share within their polypeptide sequence the epitope recognized. However, Appellant's interpretation of the claim language is inconsistent with both the usage of this limitation in the instant specification and with the meaning ascribed to the phrase by one of ordinary skill in the art at the time the invention was made.

It is again noted that the amino acid sequence of the peptide used to produce the antisera (i.e., polyclonal antibodies in a composition) of Liu et al. is present in both the hTE polypeptide of Liu et al. and instant SEQ ID NO:1.

The sequence of the immunizing peptide is 100% conserved between the hTE polypeptide of Liu et al. and instant SEQ ID NO:1. In addition, the antisera of Liu et al. binds the hTE polypeptide, indicating that the sequence of amino acids used in the immunizing peptide is available for binding in the context of the polypeptide. The polyclonal antibody in the antisera of Liu et al. must necessarily bind the polypeptide of SEQ ID NO:1 because the polypeptide of SEQ ID NO:1 contains exactly the amino acid sequence for which the antibody is specific.

Given that the antibody is the same and the sequence of amino acids bound by the antibody is the same this binding cannot be anything other than "specific".

The Examiner has given sound scientific reasons why the antisera of Liu et al. would necessarily bind the polypeptide of SEQ ID NO:1. Appellant provides no evidence to refute the Examiner's reasoning, but instead attempts by Appellant's arguments to redefine the terms of the claim to give them a meaning that is repugnant to the art.

Issues 2 and 3: Obviousness Rejections

Appellant's arguments with respect to the grounds of rejection under 35 U.S.C. 103(a) (Issues 2 and 3) rely upon the argument set forth in Issue 1 regarding the interpretation of the phrase "specifically binds". This argument has been addressed supra.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Jessica Roark

February 2, 2004

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